HFI-35

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

M4959

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 526-6002

December 6, 2000

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED
E. Thomas Arington, President
Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213

FILE NO.:01-NWJ-10

Dear Mr. Arington:

During an inspection of your facility located at 400 Campus Drive, Somerset, New Jersey, conducted by the U.S. Food and Drug Administration, between the dates of September 26 and October 19, 2000, our investigator documented serious deviations from the Good Manufacturing Practices Regulations (Title 21, Code of Federal Regulations, Part 210 and 211) in conjunction with your firm's manufacture of prescription drug products.

The deviations were presented to your firm's attention on a FDA-483, List of Observations, at the close of the inspection on October 19, 2000. These cGMP deficiencies cause your products to be adulterated within meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

The significant observations are as follows:

1. The firm failed to validate the Dissolution Test Method #FV-002 and #FV-003, used to test the product Verapamil HCL Extended Release (ER) Tablets, USP, 120 mg and 240 mg.

   A. Dissolution test data was invalidated for Batch #990801 through #990806 and Batch #991208, without conducting a complete, conclusive, or documented investigation into the cause of the failing results. All of the results were invalidated due to air bubbles being trapped in the HPLC System, at the time of the sample run. The problem continued for several months, during which batches were tested, and released.

B. Change control procedures in the laboratory failed to document test method changes to assure accurate, reliable, and reproducible results. The test method did not state whether or not a helix was to be used during dissolution testing. A [redacted] was reportedly used during method development, method validation, and daily method runs, but there is no documentation of a [redacted] being used in any of documents.

Failing S3 dissolution results for Batch #990801, as well as high dissolution results for other batches were attributed to the use of a [redacted]. The firm decided to recall Batch #990801 and #990716, due to the dissolution failure, and perform a market withdrawal of numerous other batches. The referenced batches were then retested without the use of a [redacted]. The results were considered acceptable, even though a [redacted] was used during the method development and method validation. The recall and market withdrawal was canceled.

2. There is no assurance that the manufacturing/tableting process for the product Acetaminophen and Codeine Phosphate Tablets will consistently produce tablets that meet established specifications. Batch #990807, #990103, #990707, #990709, and #990710 all failed friability specifications (specification is NMT [redacted] weight loss). In addition, there were examples of broken and chipped tablets, failing disintegration results, and out-of-specification hardness results for several other batches.

3. Failure to adequately evaluate unknown or extraneous peaks observed during chromatographic testing of Acetaminophen and Codeine Phosphate Tablets. Investigation reports were not always evaluated, and their sources or identities were not always supported by scientific data.

Investigation Report #1999-018 evaluated an extraneous peak at Retention Time 1.2 minutes observed in Acetaminophen/Codeine, Batch #990502 through #990506 HPLC Assay chromatograms. The original report concluded that the extraneous peak was not a result of glassware contamination. In a follow-up memo it concluded the peaks were due to residual detergent in the glassware.

4. Failure to follow batch manufacturing instructions during the manufacturing of Acetaminophen and Codeine Phosphate Tablets. For example:

   A. Batch manufacturing record requires that the wet granulation be dried at [redacted] for [redacted] hours. Batch #990906 was only dried for [redacted] minutes, Batch #990808 was only dried for [redacted] minutes, and Batch #991114 was dried for [redacted] minutes.

   B. Incorrect amounts of raw materials were weighed and added for Batch #990516, #990513, and #990503. Wrong amounts of Starch, Purified Water, and Providone were weighed during manufacturing.

   C. Batch #991102 of Oxycodone and Acetaminophen Capsules was incorrectly labeled as Batch #991002 and distributed.

5. There is no assurance that qualification or maintenance of the laboratory equipment can consistently produce valid and accurate analytical results in that numerous examples of test data were invalidated due to instrument malfunction.

6. The process validation for Verapamil HCl ER Tablets, 120 mg & 240 mg, and Acetaminophen and Codeine Tablets is inadequate in that the processes, when operating at the extremes of their established limits, failed to produce results within acceptable limits. Numerous batches run within the established limits failed to meet specifications ranging from assay, thickness, hardness, and friability.

7. Failure to comply with the USP, which requires that after a failing dissolution result at the L2 stage, the sample must be taken to the L3 level. For Verapamil ER Tablets, Batch #990716, an average dissolution result of 87.0% was obtained at the L2 stage at hour five, which failed to meet the specification of 55-85%. This test was not taken to the third level for additional testing.

8. There is no assurance that the laboratory HPLC columns can produce valid, reliable, and reproducible results. On numerous occasions data was invalidated due to problems attributed to the HPLC column including split peaks, distorted peaks, peak area differences, excessive peak tailing, and fluctuating retention times.

9. Method Validation Studies conducted for Acetaminophen and Codeine Tablets were incomplete in that it does not include an adequate determination of the levels at which impurities could be quantitated. The Limit of Quantitation (LOQ) for impurities was established at [redacted] which exceeds the established specification of NMT [redacted] for individual impurities. The LOQ does not demonstrate that impurities can be detected at levels below the specification.

10. Failure to follow Standard Operating Procedure (SOP) No.F14, "Time Limit on Production Operations", which states that not more than one month elapses between granulation/mixing operation and the start of a compressions/encapsulation and three months between finished product release and the filling/packaging operation. The manufacturing of Oxycodone and Acetaminophen Capsules, Batch #991203, began December 1999 and was not completed until June 2000. No hold time studies were established to support the length of time in which the batch was held.

Additionally, during the inspection there were questions raised by the Investigator concerning unknown impurities and degradants up to levels of [redacted] observed for the product Glipizide Tablets. We are aware that the specification of less than [redacted] is in the approved ANDA, but it is our concern that these impurities and degradants have not been evaluated. We suggest that all impurities at levels greater than 0.1% should be evaluated and identified.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practices Regulations. We request that you take prompt action to correct any noted violations not already corrected and undertake a comprehensive evaluation of your cGMP compliance. Failure to promptly correct these violations may result in regulatory action without further notice. This includes seizure and/or injunction.

Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. In addition, pending new drug applications (NDA's) or export approval requests may not be approved until the aforementioned violations are corrected.

We have received your written response dated October 31, 2000, regarding the inspectional observations noted on the FDA-483. In your response regarding Observation No.1, it states that the firm will withhold release of any new lots of Verapamil HCL ER Tablets until you evaluate the use of the [redacted] in the dissolution method. Please notify us when you complete your evaluation and resume distribution of Verapamil HCL. We will evaluate the implementation and the adequacy of your proposed corrective actions during the follow-up inspection of your firm.

You should notify this office in writing within 15 working days of receipt of this letter, with the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. Please provide us with updates of the current status of your corrective actions. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to the Food and Drug Administration, New Jersey District Office, 10 Waterview Blvd, 3rd Floor, Parsippany, New Jersey 07054, Attention: Andrew Ciaccia, Compliance Officer.

Very truly yours,

Douglas I. Ellsworth

DOUGLAS I. ELLSWORTH
District Director
New Jersey District Office

AC:slm